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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,521	03/19/2001	Caroline Kreutzer	P 278416 980183 BT-CIP	6186

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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/03/2003

24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/810,521

Applicant(s)

KREUTZER ET AL.

Examiner

Delia M. Ramirez

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,5-18 and 21-32 is/are pending in the application.
- 4a) Of the above claim(s) 5-15,17,18,21 and 24-26 is/are withdrawn from consideration.

5) ☒ Claim(s) 22 and 23 is/are allowed.

6) ☒ Claim(s) 1,3 and 27-32 is/are rejected.

7) ☒ Claim(s) 16 is/are objected to.

8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

Claims 1, 3, 5-18, 21-32 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's amendment of claims 1, 3, 22-23, and 28-32 in Paper No. 21, filed on 3/19/2003 is acknowledged.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/19/2003 has been entered.

As indicated in previous Office Action Paper No. 18, mailed on 11/19/2002, claims 5-15, 17, 18, 21, and 24-26 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an invention non-elected without traverse in Paper No. 12, filed 4/8/2002. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

1. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to GERMANY 199-31-314.8 filed on 5/7/1999.
2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/353,608 filed on 7/14/1999.

Terminal Disclaimer

3. The terminal disclaimer filed on 10/15/2002 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6200785 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Drawings

4. The drawings have been reviewed and are approved by a draftsman under 37 CFR 1.84 or 1.152.

Claim Objections

5. Claims 1 and 30 objected to because of the recitation of "L-lysine producing bacteria". For clarity, it is suggested that the term be replaced with "An L-lysine producing bacterium". Appropriate correction is required.
6. Claims 1 and 29 are objected to because of the recitation of "promotor". It is suggested that the term be replaced with "promoter". Appropriate correction is required.

7. Claim 1 is objected to because of the recitation of "wherein overexpression of said pyc gene....of said pyc gene wherein overexpression of said dapA gene..". For clarity, it is suggested that the term "and" or a comma, be inserted in between the terms "pyc gene" and "wherein".

Appropriate correction is required.

8. Claims 1 and 29 are objected to because of the recitation of "MA20". It appears that the term "MA20" is a typographical error since according to the specification, SEQ ID NO: 6 represents an MA16 mutation. Appropriate correction is required.

9. Claims 3, 27-29, 31-32 are objected to because of the recitation of "Bacteria of claim #". It is suggested that the term be replaced with "The bacterium of claim #" since said bacterium has already been defined in a previous claim. Appropriate correction is required.

10. Claim 16 is objected to because of the recitation of "Escherichia coli". For clarity, it is suggested that the term be replaced with "An Escherichia coli". Appropriate correction is required.

11. Claim 29 is objected to because of the recitation of "insterted". It appears that the term is a typographical error. For examination purposes, it will be assumed that the intended meaning of the term is "inserted". Appropriate correction is required.

12. Claim 29 is objected to because of the recitation of "a aecD..gene". For clarity, it is suggested that the term be replaced with "an aecD...gene". Appropriate correction is required.

13. Claim 30 is objected to because of the recitation of "encoding lysine export carrier". For clarity, it is suggested that the term be replaced with "encoding a lysine export carrier".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1, 3, 27-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
16. Claim 1 is indefinite in the recitation of “synthase activity above the level of a wild type *Corynebacterium glutamicum*” as it is unclear how one can compare synthase activity with a bacterium. If the intended comparison is between synthase activity when overexpression takes place versus synthase activity when no overexpression takes place, it is suggested that the term be amended to recite “synthase activity above the level of that found in a wild type *Corynebacterium glutamicum*”. For examination purposes, the suggested language will be used. Correction is required.
17. Claim 3 is indefinite in the recitation of “overexpression of said *LysE* gene is achieved by increasing the copy number of *LysE* genes” as it is unclear and confusing. As written, it appears that overexpression of the *C. glutamicum* *LysE* gene is achieved by increasing the copy number of other *LysE* genes which may not be from *C. glutamicum*. It is suggested that the term be amended to recite “overexpression of said *LysE* gene is achieved by increasing the copy number of said gene” or similar. For examination purposes, the suggested language will be used. Correction is required.
18. Claim 28 is indefinite in the recitation of “aspartate kinase is resistant to inhibition and/or threonine” as it is unclear what the meaning of the term is. As written, it appears that aspartate

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kinase can be resistant to threonine. For examination purposes, it will be assumed that the intended meaning of the term is "aspartate kinase is resistant to inhibition by lysine and/or threonine". Correction is required.

19. Claim 29 is indefinite in the recitation of "wherein said dapA gene including a dapA promotor selected from the group consisting of:....wherein said dapA gene, including said dapA promotor is insterted into a aecD (amino ethyl cysteine degrading) gene..." as it is unclear and confusing. Applicants argue that the claim as amended should render this rejection moot, however, the Examiner disagrees with Applicant's contention for the following reasons. First, the term "wherein said dapA gene including a dapA promoter" is unclear since one cannot determine if the meaning of the term is "dapA gene and a dapA promoter" or "dapA gene or a dapA promoter". Furthermore, there is no linking clause between the first recitation of "wherein said dapA" and the second recitation of said term. In addition, the term "insterted into a aecD....gene of C. glutamicum" is unclear since one cannot determine what is being inserted, the dapA gene, the dapA promoter, or both. Finally, it appears from the specification that the dapA gene is linked to the aecD gene and not inserted into the aecD gene as recited. It is noted that the presence of the aecD gene would allow for the C. glutamicum cell to utilize S-(beta-Aminoethyl)-cysteine (AEC) as an alternative nitrogen source. Therefore, if the dapA gene is inserted into the aecD gene, this will destroy the ability to use AEC. Since it is unclear from the claim if the insertion of the dapA gene and its promoter is intended to eliminate AEC utilization and the specification does not seem to indicate the inactivation of the aecD gene by insertion of the dapA gene, for examination purposes, the claim will be interpreted as being drawn to the

bacterium of claim 1 further comprising the *C. glutamicum* aecD (amino ethyl cysteine degrading) gene. Correction and/or clarification is required.

20. Claims 27, 30-32 (claim 28 dependent thereon) are indefinite in the recitation of "overexpressed" since it is a relative term, no standard for ascertaining the requisite degree has been provided and one of skill in the art would not be reasonably apprised of the scope of the invention. This rejection was applied to claims 27, 30-32 in previous Office Action Paper No. 18, mailed on 11/19/2002.

Applicants argue that the inclusion of the term "wild-type" further defines the scope of the claims. In addition, Applicants argue that the claims have been amended to indicate that "overexpression" refers to a level above that produced using a wild type *C. glutamicum*. While Applicant's arguments have been fully considered, they are not deemed persuasive to overcome the rejection as it applies to claims 27-28, 30-32. It is noted that neither claim 27 nor claim 30 recite a definition of the term "overexpressed" as asserted. Furthermore, the term "wild type" in claim 30 defines which *pyc* gene is to be "overexpressed" but does not define the term "overexpressed". For examination purposes, it will be assumed that the term "overexpressed" refers to a gene which is expressed at a level which is higher than its normal expression level in a wild-type *C. glutamicum*. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

21. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claims 27-28, 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

23. This rejection has been discussed at length in Paper No. 18 and is now applied to amended claims 27-28 and 30-32 for the reasons of record.

24. Applicants argue that the *C. glutamicum* *pyc*, *lysC*, and *lysE* genes are well known in the prior art and that the teachings of the prior art in conjunction with the teachings of the specification in regard to overexpression by increasing the copy number of the genes as well as the amendments filed, should render the claims neither vague nor indefinite.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. It is noted that while the instant claims have been rejected under 35 USC, 112 second paragraph as being indefinite, those rejections and any arguments presented by Applicants have already been addressed above. In regard to the instant written description rejection, while it is agreed that *C. glutamicum* *pyc*, *dapA*, *lysC* and *lysE* are known in the prior art, claims 27-28 and 30-32 are directed to a bacterium wherein these genes are overexpressed by any means and not just by increasing the copy number of the desired gene. As indicated in previous Office Action Paper No. 22, mailed 4/18/2003, the specification discloses at page 7 that overexpression can be achieved by altering the promoter and the regulatory region or the ribosome binding site of the desired gene but there is no disclosure of which mutations in the promoter, regulatory region, or the ribosome binding site of the recited genes, will result in

overexpression of such gene. Therefore, it is unclear as to how one of skill in the art can reasonably conclude that the claimed invention is adequately described if mutant genes essential to practice the claimed invention have not been disclosed in the specification or the prior art. The instant disclosure does not provide sufficient description of a representative number of species, as encompassed by the genera of mutant genes recited in the claims, to put one of skill in the art in possession of all attributes and features of all species within the claimed invention.

25. Claims 27-28 and 30-32 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *C. glutamicum* cell wherein the *C. glutamicum* *pyc* gene, *C. glutamicum* *dapA* gene, *C. glutamicum* *lysE* gene are overexpressed by increasing the copy number of such genes, does not reasonably provide enablement for (1) said *C. glutamicum* cell further capable of overexpressing the *C. glutamicum* *lysC* gene by any means or (2) said *C. glutamicum* cell further capable of overexpressing a *C. glutamicum* *lysC* gene which has been mutated to encode an aspartate kinase which is resistant to inhibition by lysine and/or threonine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

26. This rejection has been discussed at length in Paper No. 18 and is now applied to amended claims 27-28 and 30-32 for the reasons of record.

27. Applicants argue that the claims as amended are fully enabled by the specification. Specifically, Applicants refer to overexpression of the *pyc* gene through increasing the copy number of the *pyc* gene.

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28. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. As indicated above, claims 27-28 and 30-32 are directed to a bacterium wherein the *C. glutamicum* *pyc*, *dapA*, *lysE* and *lysC* genes are overexpressed by any means and not just by increasing the copy number of the desired gene. While the specification discloses that overexpression can be achieved by altering the promoter, the regulatory region or the ribosome binding site of the desired gene, the specification fails to disclose which are the modifications (i.e. substitutions, deletions or insertions) in the promoter, the regulatory region or the ribosome binding site, which would result in overexpression of said genes. As such, one of skill in the art would have to go through the burden of undue experimentation to (1) isolate the promoter, regulatory region or the ribosome binding site of the recited genes if they are unknown and/or (2) create an extremely large number of modifications in the promoter, regulatory region and/or ribosome binding site and test which ones would result in overexpression of the gene. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

31. Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peters-Wendisch et al. (DE 198-31-609-A1, cited in the IDS) in view of Cremer et al. (EP-0-435-132-A1, cited in the IDS), Vrlije et al. (DE 195-48-222-A1, cited in the IDS), and Araki et al. (EP 0-854-189-A2, cited in the IDS).

32. This rejection, which was applied to claims 30-31, has been discussed at length in Paper No. 18, mailed on 11/19/2002 and is applied to claim 32 for the reasons set forth below.

33. Applicants argue that the cited documents neither alone or in combination teach or suggest the simultaneous enhancement of either (1) the *pyc*, *dapA* and *lysE* or (2) *pyc*, *dapA*, *lysC* and *lysE*, using the *dapA* promoter as set forth in SEQ ID NO: 5 or SEQ ID NO: 6.

Therefore, Applicants conclude that the Examiner has failed to establish a prima facie case of obviousness and request the withdrawal of the rejection.

34. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. Claim 30, as written, is drawn to a *C. glutamicum* cell which is capable of overexpress the *C. glutamicum pyc*, *dapA* and *lysE* genes by any means. Claim 31 adds the limitation that said cell be also capable of overexpressing the *C. glutamicum lysC* gene whereas claim 32 adds the limitation that the *lysC* gene overexpressed encode a mutant aspartate kinase

which is resistant to inhibition by lysine and/or threonine. None of claims 30-32 require the use of the dapA promoters as set forth in SEQ ID NO: 5 or 6.

As indicated in previous Office Action Paper No. 18, Peters-Wendisch et al. teaches that overexpression of the *C. glutamicum* pyc gene (pVWEX1pyc) in *C. glutamicum* (DG52-5 strain) resulted in significant increase of L-lysine in the medium (pages 5-6; Table 2, DG52-5(pVWEX1pyc)). Cremer et al. teaches the overexpression of the *C. glutamicum* dapA and lysC genes in *C. glutamicum* (page 5, lines 15-32) which resulted in increased production of L-lysine relative to the overexpression of the dapA or lysC genes alone (Table 2, page 7). Vrljic et al. teaches that overexpression of the *C. glutamicum* lysE gene in *C. glutamicum* resulted in increased yields of L-lysine in the medium since lysine transport to the medium was enhanced (page 5; Figures 3 and 4). Araki et al. teaches that the overexpression of dapA, a mutant lysC, dapB, lysA, and aspC genes simultaneously resulted in increased production of L-lysine after 72 hours of growth (Table 4, last two entries, page 18). The mutant lysC used by Araki et al. encodes a *C. glutamicum* (also known as *Brevibacterium lactofermentum* ATCC 13869, page 4, line 11; page 4 line 55-page 5, line 13, SEQ ID NO: 3-7 sequence listing under organism) aspartate kinase which is resistant to inhibition by lysine and threonine (page 2, lines 54-57; page 3 line 37, plasmid pCABL).

It would have been obvious to one of ordinary skill in the art to construct a *C. glutamicum* bacterium which is capable of overexpressing the *C. glutamicum* pyc, lysE, dapA and lysC genes by combining the teachings of Peters-Wendisch, Cremer, Vrljic and Araki. One of ordinary skill in the art is motivated to combine these teachings for the benefit of increasing lysine yields, since as demonstrated by Araki and Cremer, the combined overexpression of two

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or more genes that increase production of lysine is beneficial for increasing lysine yields. One would have a reasonable expectation of success at transforming a *C. glutamicum* cell with expression vectors comprising the *C. glutamicum* *pyc*, *lysE*, *dapA* and mutant *lysC* gene because each of the references cited teach the successful transformation of *C. glutamicum* with vectors comprising each of the *C. glutamicum* genes mentioned above. Furthermore, each of the references cited above teach the improvement of lysine production when such genes are overexpressed. Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

35. Claims 16, 22 and 23 appear to be allowable over the prior art of record.

Conclusion

36. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

37. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of

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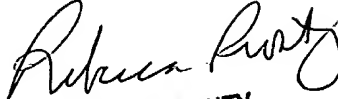
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a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
May 28, 2003


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1800
(600)